Continuing education

18F-FDG-PET/CT in lymphoma: Two decades of experience

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ABSTRACT

The use of 18F-FDG-PET/CT has changed the management of patients with lymphoma for the last two decades. This technique improves initial staging of the disease, making a prognostic approach and appropriate treatment planning, as well as monitoring therapy response of lymphoma. However, there are still controversial issues in medical literature that impact on daily clinical practice. This comprehensive literature review summarizes the current information regarding the potential use of 18F-FDG-PET/CT in patients with lymphoma, highlighting the main applications and the current dilemmas for the nuclear medicine physicians at the time of the evaluation of these studies, trying to standardize criteria for its assessment, particularly in restaging and therapy monitoring.

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18F-FDG-PET/TC en linfoma: dos décadas de experiencia

RESUMEN

El uso del 18F-FDG-PET/TC ha introducido cambios relevantes en el manejo de los pacientes con linfoma en las últimas dos décadas. Esta técnica de imagen funcional permite mejorar la estadificación inicial de la enfermedad, realizar una aproximación pronóstica y planificar un tratamiento adecuado, monitorizar la respuesta a las terapias instauradas y hacer un seguimiento para el diagnóstico de recidiva y reestadificación del linfoma. Sin embargo, aún existen controversias sobre el tema en la literatura médica que repercuten en la práctica diaria. Esta profusa revisión bibliográfica resume la información actual sobre el uso potencial de 18F-FDG-PET/TC en pacientes con linfoma, destacando sus principales aplicaciones y los dilemas que se presentan al evaluar este tipo de estudios, intentando estandarizar criterios para su valoración, particularmente en la reestadificación y monitorización de la terapia.

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Introduction

Lymphomas make up a heterogeneous group of neoplastic diseases of lymphocitary origin. These malignant lymphoproliferative processes are clonal B-cell, T-cell or natural killer (NK) cells tumors in different stages of differentiation.

Lymphomas represent 6% of all neoplasms and are responsible for 3% of the mortality by oncological processes.1 The incidence of lymphomas in Spain is up to 4% each year, with around 6000 new cases being diagnosed annually, mostly non-Hodgkin lymphomas (NHL). This growing incidence is attributable to the increase in situations of immunosuppression [human immunodeficiency virus (HIV), organ transplantation], an oncogenic effect associated with different viral infections [Epstein–Barr virus (EBV), hepatitis C virus (HCV)], environmental changes (antibiotics, chemical agents, vaccines, radiations), etc. together with a longer life expectancy and subsequent ageing of the population at risk.2-5 Lymphomas are somewhat more frequent in men than in women and more common in 2 age groups: from 15 to 40 years of age (being more frequent between 25 and 30 years) and after the age of 55 years.

Thomas Hodgkin published the first description of lymphoma in 1832, specifically in the form with his name, Hodgkin’s lymphoma (HL).6 In the following 50 years, Virchow, Cohnheim and Billroth, defined other lymphomas different from HL, originally being called lymphosarcomas. Since then many other forms of lymphoma have been described and different classifications have been proposed based on morphological criteria.7-11 In 1994, the International Study Group of Lymphoma established a consensus in the classification based on morphology and immunological, molecular and genetic techniques in an attempt to obtain an internationally accepted classification: the Real European-American Classification of Lymphoid Neoplasms (REAL). This classification was adapted by the World Health Organization (WHO) in 1997, with modifications and updates being made in 2001 and 2008. The WHO classification of 2008, which was based on the previous REAL classification of 1994, is currently recognized worldwide as having a high grade of precision and consensus in the diagnosis of the different varieties of lymphoma, defining the entities according to their histology, on
the clinical basis, and immunophenotype and genetics into 4 large groups by cell types (Table 1). There are important differences among the principal types of lymphoma. Hodgkin’s disease (HD) is characterized by the presence of a tumor mass formed by inflammatory cells including malignant cells (Reed–Sternberg cells) and presents a pattern of dissemination by continuity, with infrequent extra lymph node involvement. The origin of NHL is in the B- or T-cells. Extra-lymphatic involvement is much more frequent than in HD and the lymph node dissemination is “more disorderly”, often compromising peripheral lymph nodes (inguinal, axillary). The definitive diagnosis of malignancy and classification of the different subtypes is based on meticulous interpretation of the preparation obtained of the biopsied tissue.12

Positron emission tomography and its application in lymphomas

PET as a diagnostic imaging technique that demonstrates changes in tissular metabolic activity has shown to be a very useful tool in the evaluation of this type of tumors. Since its introduction in the clinical setting to the current use of hybrid PET/CT equipment its use has significantly modified the management of patients with lymphoma. The information provided by this technique allows improvement in the initial staging, determination of the prognosis and the planning of an adequate treatment, monitoring the response to the therapy implemented and carrying out the follow-up to diagnose recurrence and restaging of lymphoma.13,14 Thus, in 2007, a report by the National Comprehensive Cancer Network (NCCN) already mentioned that 18F-FDG-PET/CT may be used to evaluate lymphomas in up to more than 50% of the total number of studies performed in reference institutions.15

The radiotracer most commonly used, 18F-FDG, allows evaluation of lymphoproliferative processes, obtaining images and quantifying the glycolytic metabolism within the tumor cell. However, it is known that the “avidity” of FDG by the tumor cells varies due to the different grades of malignancy and proliferative activity of each histological subtype, especially in NHL (Table 2). A direct relationship has been reported between the grade of malignancy and FDG uptake, with the consequent lower diagnostic yield of PET in indolent or low grade lymphomas.16–18

| Table 1  |
The WHO classification of lymphomas (Jaffe11).

<table>
<thead>
<tr>
<th>Mature B-cell neoplasms</th>
<th>Mature T and NK cell neoplasms</th>
<th>Hodgkin’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia/well differentiated</td>
<td>Prolymphocytic T-cell leukemia</td>
<td>Hodgkin’s lymphoma Nodular lymphoma of lymphocytic predominance</td>
</tr>
<tr>
<td>Lymphomatous granulomatosis</td>
<td>T-cell lymphoma with large granular lymphocytes</td>
<td>Classical Hodgkin’s lymphoma Nodular sclerosis</td>
</tr>
<tr>
<td>Large intravascular cell and large B-cell ALK+ lymphoma</td>
<td>Chronic lymphoproliferative NK cell disease</td>
<td>Mixed cellularity</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>Aggressive NK cell leukemia</td>
<td>Rich in lymphocytes</td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>Lymphoproliferative systemic T-cell disease</td>
<td>Lymphoid depletion</td>
</tr>
<tr>
<td>Primary cutaneous centrofollicular lymphoma</td>
<td>Vacciniforme-like lymphoma</td>
<td>Post-transplant lymphoproliferative disease (PTLD)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Adult T-cell leukemia/lymphoma</td>
<td>Early lesions</td>
</tr>
<tr>
<td>Diffuse non-specified large B-cell lymphoma</td>
<td>Extramedullary NK/T-cell lymphoma (nasal)</td>
<td>Plasmacytic hyperplasia</td>
</tr>
<tr>
<td>Lymphoma staging by PET/CT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of lymphoma</th>
<th>% Patients with uptake</th>
<th>Uptake intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td>100</td>
<td>High</td>
</tr>
<tr>
<td>Classical HD</td>
<td>100</td>
<td>Moderate-high</td>
</tr>
<tr>
<td>Nodular HD with lymphocytic predominance</td>
<td>100</td>
<td>Moderate-high</td>
</tr>
<tr>
<td>Aggressive NHL</td>
<td>97</td>
<td>Moderate-high</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>100</td>
<td>High</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>90</td>
<td>Low–high</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>100</td>
<td>High</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>100</td>
<td>Moderate</td>
</tr>
<tr>
<td>Indolent NHL</td>
<td>95</td>
<td>Low–high</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>100</td>
<td>Low–moderate</td>
</tr>
<tr>
<td>Lymphoplasmocytic lymphoma</td>
<td>100</td>
<td>Low–moderate</td>
</tr>
<tr>
<td>Marginal zone nodal lymphoma</td>
<td>100</td>
<td>Null–high</td>
</tr>
<tr>
<td>Marginal zone extranodal lymphoma (MALT)</td>
<td>54</td>
<td>Null–high</td>
</tr>
<tr>
<td>Small cell lymphocytic lymphoma</td>
<td>83</td>
<td>Null–high</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>40</td>
<td>Null–moderate</td>
</tr>
</tbody>
</table>

Modified from Refs. 16–18.

* The take the cytological grade of follicular NHL into account, grade III follicular NHL is considered as aggressive, presenting moderate–high avidity for FDG. However, grades I and II (considered to be indolent) present low–moderate uptake.
demonstrated a better diagnostic yield to detect lymph node and extra lymph node involvement prior to treatment, allowing more correct staging of lymphomas according to the Ann Arbor classification with the Cotswolds modification (Table 3).

Multimodal PET/CT examination provides additional advantages in staging compared to CT or PET separately, demonstrating a greater number of lesions, mainly at an extra lymph node level in HD, DLBCL, follicular lymphomas (FL) and mantle cell lymphoma (MCL). It has been calculated that detectability by this technique is almost 15% greater compared to conventional CT since this method mainly depends on the size and morphology of the lesions. On comparing PET/CT with conventional CT in the staging of the subtypes of lymphomas mentioned, a sensitivity of 94% vs. 88% and a specificity of 100% vs. 86% have been reported, respectively, thereby demonstrating greater precision of the functional study due to the presence of lesions with metabolic alterations which do not yet present radiological manifestations. The multimodal method is considered to modify the initial staging in 20–40% of these patients, although a change in the therapeutic strategy is made in only half of the cases. Likewise, pretreatment performance in HD, FL and DLBCL make comparison possible with studies undertaken during the course of the therapy initiated, that is, the interim evaluation and after finalization of treatment. A baseline study is therefore mandatory (Fig. 1).

Few studies have been published on the use of PET/CT and its precision in the staging of indolent lymphomas. Studies on only the PET technique have reported that these subtypes present variable avidity for FDG with less avidity compared with that of aggressive HD and NHL. This has led some authors to recommend the exclusive use of initial diagnostic CT for the staging of indolent NHL such as, for example, marginal zone small cell lymphocytic lymphomas and that associated with the mucosa (MALT), performing PET only in clinical studies. Nonetheless, a recent study by Fueger et al. comparing PET, CT and PET/CT left the door open for greater investigation of the utility of functional studies in low grade lymphomas, complementing these with CT with intravenous contrast for the detection of lymph node and extra lymph node lesions which do not present FDG uptake.

In general, PET is considered to have good capacity for the evaluation of bone marrow involvement by lymphoma, even in cases with a negative biopsy. However, when the involvement is limited or in indolent lymphomas, the yield of functional imaging is lower. The yield increases considerably with PET/CT equipment, achieving a sensitivity and specificity of 91% and 90%, respectively, and thus, directing the best choice for the localization for biopsy. Nonetheless, it should be taken into account that in patients with HD, diffuse increased uptake of the bone marrow pretherapy does not necessarily signify involvement of the same since this may be due to a reactive myeloid hyperplasia which may even present focally.

With respect to the CT component of the multimodal technique, the use of intravenous contrast in the staging of lymphoma is controversial. Different work groups have compared the findings of PET/CT with and without intravenous contrast and found high concordance between the low dose CT findings (approximately 80 mAs in the multimodal study) and those of standard and contrast dose CT (Kappa 0.9), concluding that PET/CT may be performed for the staging of lymphomas using a CT component at a low dose and without intravenous contrast. Other authors also support this recommendation which reduces unnecessary exposure to radiation, mainly in HD, FL and DLBCL, reserving the use of higher dose and contrast-enhanced CT for selected cases. Another alternative may be the use of PET/CT with intravenous contrast first for the initial staging and then continue the follow-up with low dose studies without contrast, except in cases with a negative PET at the onset.

### Table 3

Ann Arbor classification (Cotswolds modification) for the staging of lymphomas.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement of a single lymph node region or lymphoid structure (i.e. spleen, thymus, Waldeyer ring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site: the hilum include one on each side); the number of sites is indicated with a subset (i.e. I1, I3)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of lymphatic regions or lymphatic structures on both sides of the diaphragm.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Upper abdomen (spleenic, celiac, portal).</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Involvement of extranodal sites beyond those indicated as E.</td>
</tr>
</tbody>
</table>

**Applicable to any stage:**
- A: no B symptoms.
- B: fever, nocturnal sweats, loss of more than 10% of body weight in previous 6 months.
- C: Bulky disease: mediastinal widening >1/3 measured at the T5–6 level, or mass >10 cm.
- D: Involvement of a single extranodal site contiguous or next to the known lymph node localization.
- S: Splenic involvement.
Evaluation of therapeutic response of lymphomas by 18F-FDG-PET/CT

Different patients with the same tumor pathology and a similar clinical-histological substrate may show very different results following treatment. When we evaluate this phenomenon we are referring to tumor response. Thus, the aim is to validate the efficacy of the treatments applied, identify ineffective treatments early, establish objective criteria of response and determine the real extension of the disease after therapy.\textsuperscript{29,35}

The use of 18F-FDG PET is essential at the end of treatment in patients with HD and DLBCL since the intention of the therapy is curative and therefore it is necessary to know whether complete response has been achieved. In addition, the possible persistence of disease after treatment shown by 18F-FDG-PET/CT constitutes an independent prognostic factor of the initial stage of the disease.\textsuperscript{36} Even in patients with HD receiving treatment with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), recent studies\textsuperscript{37,38} have shown that the evidence of uptake in interim studies has prognostic value. At present, restaging is one of the principal applications of 18F-FDG PET in lymphoma, particularly in HD and DLBCL. Restaging would be adequate in other types of incurable lymphomas (indolent) only when the rate of therapeutic response is evaluated and if a baseline study has been performed.\textsuperscript{39}

The study should not be carried out before 3 weeks after the completion of treatment, preferably being performed from 6 to 8 weeks after chemotherapy (ChT) or immunoChT and from 8 to 12 weeks after the finalization of radiotherapy (RDT) or RDT-ChT. The usual criteria of response are those described by Cheson and Juweid.\textsuperscript{39–41}

The negative predictive value (NPV) is high (>80%) for both HD and DLBCL, with a similar value to that of helical CT.\textsuperscript{40–42} Based on the type of lymphoma and the efficacy of the therapy, false negative results vary from 10 to 20% (similar to CT and MR), being mainly related to the incapacity to detect microscopic disease conditioning future relapse, although they may also influence other factors such as the resolution of the equipment and the technique.

The positive predictive value (PPV) of 18F-FDG-PET shows something more variable, and generally lower, results, being in the range of 70–80% in DLBCL and from 60 to 70% in HD. In regard to justification for the greater number of false positives in HD compared to DLBCL, the more frequent use of RDT may produce actinic inflammatory changes. Other factors may be the possible presence of infection, inflammation, sarcoidosis, activated brown fat and thymic hyperplasia, mainly in young patients. In both HD and DLBCL nearly one third of the patients present a positive 18F-FDG-PET/CT post-therapy, presenting risk of progression or recurrence in 60–70% of the cases. From another point of view, 30–40% of the cases with a final positive 18F-FDG-PET/CT neither progress nor present recurrence, thereby making histological confirmation of this possible site of disease necessary prior to the initiation of rescue ChT.\textsuperscript{43,44}

The results of restaging by CT are substantially lower with 40% of PPV for NHL and 20% for HD. These results are probably related to the difficulty in carrying out a differential diagnosis between residual mass (fibrosis), necrosis and viable tumor, from a morphological point of view, with a great advantage with 18F-FDG-PET/CT (provided that adequate times are respected for the evaluation of response).\textsuperscript{42,45} Thus, in the post-treatment assessment one third of the patients with DLBCL present residual mass which, according to metabolic criteria, are characterized as negative for the persistence of disease in more than two thirds of the patients, with a relapse rate of less than 15–20%.\textsuperscript{41–46} In the case of patients with HD, around 70% present residual mass by CT, two thirds of which show negative metabolic results and relapse in less than 10%. The International Harmonization Project on lymphoma has presented certain recommendations with the intention to reduce the number of false positive results in 18F-FDG-PET/CT studies post-treatment.\textsuperscript{39,40} These recommendations emphasize the interval of assessment: not less than 3 weeks after ChT and from 8 to 12 weeks post-RDT. This project recommends visual examination as sufficient to evaluate response, considering any uptake in a localization not related with physiologic anatomic activity as positive. In this way a cut off point for SUVmax is not necessary: it may be considered that in any lesion with a transverse diameter greater than 2 cm the uptake is positive if it exceeds the mediastinal vascular activity and for a size between 1.1 cm and 1.9 cm if it exceeds the activity of the surrounding tissue. However, some groups have reported better results, particularly in the PPV and precision, on the introduction of semiquantitative assessment with a cut-off of SUVmax of 2.5 g/ml, with greater interobserver reproducibility.\textsuperscript{42}

In some studies the inclusion of evaluation by 18F-FDG-PET/CT in aggressive NHL treated with antracycline produced a significant modification in the proportion of results in complete remission versus partial response, with a better relationship with the disease-free period. Thus, routine assessment of response to treatment is considered necessary.\textsuperscript{23} Evidence of greater precision led to a review of the criteria of evaluation of response in HD as well as in aggressive NHL. The guidelines of the International Workshop Criteria were reviewed in 2007 and incorporated immunohistochemistry, flow cytometry and 18F-FDG-PET/CT into the evaluation of response to treatment.\textsuperscript{36}

The type of response to treatment continues to be classified based on the morphological criteria of CT but takes into account either the positivity or non-uptake in 18F-FDG (Table 4):

- Therefore, complete response is considered whenever the residual mass of any size is PET negative in combination with a negative bone marrow biopsy and clinical-analytical data of absence of disease.
- In partial response there is a >50% reduction in the result of the sum of the greatest diameters of the 6 nodules or dominant masses (not necessarily the same in each study), absence of new lesions but persistence of significant uptake of glucose in at least one of the lesions (Fig. 2).
- Patients with stable disease are in an intermediate stage between partial response and disease progression and also show positive PET in at least one of the residual lesions.
- Disease progression is considered with the presence of a ≥50% increase in the sum of the diameters of any basal lymph node lesion or any other splenic or hepatic nodule. However, the appearance of any new lesion ≥1 cm in its short axis is also a criterion of progression, requiring positive PET only for new lesions with a diameter ≥1.5 cm since smaller lymphomatous lesions with moderate FDG avidity may be negative.

The old concept of uncertain complete response has been eliminated because the residual mass or persistence is classified metabolically in complete or partial response.\textsuperscript{39} It is important to underline that these criteria are validated for DLBCL and HD but not for other histology types.\textsuperscript{44} Likewise, it is recommended to biopsy the foci in patients with treated DLBCL showing positivity prior to modifying the treatment schedule.

Monitization of therapy by 18F-FDG-PET/CT in lymphomas

This is called interim evaluation (intermediate) to that performed early in the treatment, after 2 or 4 cycles and is aimed at obtaining reliable data of response which will allow confirmation or safe modification of the therapy implemented.
Table 4
Evaluation of the type of lymphoma response for clinical trials.

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Lymph node masses</th>
<th>Spleen and liver</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) Mass of any size with FDG avidity in the baseline study, with negative PET. (b) Variable FDG avidity or PET negative, but with regression to normal size in the CT.</td>
<td>Not palpable, disappearance of nodules</td>
<td>Disappearance of the infiltration, if the morphology is undetermined the immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PD or relapse</td>
<td>Any new lesion or increase ≥50% of the minimum size of any baseline lesion</td>
<td>Appearance of new lesion &gt;1.5 cm in any axis. Increase ≥50% in SMD or the maximum diameter of a lymph node identified in the baseline study &gt;1 cm in the short axis. PET positive lesions if the lymphoma has avidity for FDG or was positive prior to treatment</td>
<td>Increase &gt;50% from the minimum size in the SMD of the basal lesions</td>
<td>New or recurrent infiltration</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable lesions without the appearance of new localizations</td>
<td>Reduction ≥50% in the sum of maximum diameters (SMD) of the 6 dominant masses without an increase of the remaining masses. (a) PET+ in 1 or more lesions with FDG avidity in the baseline study. (b) Variability in FDG uptake or negative PET with regression in the CT.</td>
<td>Reduction ≥ 50% in the SMD of nodules (for a simple nodule the greater transverse diameter is taken), without an increase in size of the liver or spleen.</td>
<td>Irrelevant if positive prior to therapy, requiring specification of the cell type</td>
</tr>
<tr>
<td>SD</td>
<td>Impossibility to classify as RC/PR or DP</td>
<td>(a) PET+ prior to treatment; with FDG uptake in baseline localizations without the appearance of new foci on CT and PET. (b) Variability in FDG avidity or negative PET, with no change in size of the previous CT lesions</td>
<td>Not palpable, disappearance of nodules</td>
<td>Disappearance of the infiltration, if the morphology is undetermined the immunohistochemistry should be negative</td>
</tr>
</tbody>
</table>

SD, stable disease; PD, progression disease; CR, complete response; PR, partial response; SMD, sum of maximum diameters. Modified from Ref. 49.

Fig. 2. 18F-FDG-PET/CT for the evaluation of response to treatment. (A) 56-year-old male diagnosed with DLBCL. Pathologic supra- and infradiaphragmatic lymph node hypermetabolism as well as extranodal bone involvement were observed in the vertebral spine and with an extensive lesion in the left psoas iliac region in basal stage IV. (B) 18F-FDG-PET/CT after finalization of ChT demonstrated a >50% reduction in the maximum diameters of the lymph node and extra lymph node lesions >50% as well as in the intensity of uptake in relation to partial response to treatment.

Interim 18F-FDG-PET/CT evaluation provides information related to the prognosis of final response to ChT treatment and/or immuno-ChT because of its elevated NPV (>80% for NHL and >90% for HD). It may be considered as an independent prognostic factor similar to the baseline stage of the disease or the International Prognostic Score. In addition to other variables such as histology and the grade of aggressivity and the different treatments applied a prognostic profile of the period free of disease and overall survival may be made. This qualitative interim assessment is valid for both patients with HD and those with aggressive NHL. Several studies have demonstrated that interim evaluations may be as precise as evaluation after finalization of treatment, with the exception of the low PPV in patients with HD (approx. 30%), albeit with a NPV >95%.45,46

There is great debate with respect to the criteria of evaluation of interim 18F-FDG-PET/CT and its threshold of positivity. Successive recommendations published since at least 2005 have been aimed at reducing the number of false positive results. Hutchings et al. consider all minimum residual uptakes [mild uptake which slightly exceeds that of the background in a previously known lesion, denominated minimal residual uptake (MRU)] as negative, besides observing that these patients present a very good prognosis of final response. In 2007, Gallamini et al. proposed that MRU could be considered as an uptake that is lower than, equal to or
slightly greater than mediastinal vascular activity. More recently, Barrington et al. reported a significant increase in the PPV without affecting the NPV using more flexible criteria in the evaluation of uptake in lesions already present in the baseline study. These authors described how the activity that is equal to or slightly higher than normal hepatic uptake becomes negative, associating other criteria proposed by the International Harmonization Project including those assessed by CT.

Following the First International Workshop on PET in lymphoma a 5-point classification of the intensity of FDG uptake with respect to the mediastinum and the liver as organs of reference grouped in the London scale (Table 5) was proposed for the interim study. Nonetheless there are still discrepancies with the use of this scale regarding the cut-off point that should be used as the threshold of positivity: Barrington et al. consider grades 4 and 5 as positive while Le Roux et al. only consider grade 5 uptake, even after the fourth cycle (Fig. 3).

Mild residual uptake may be related to inflammatory changes in response to treatment and not to residual tumor, which may be seen with the disappearance of these foci on performing the evaluation after the end of the therapy. The adoption of “liberal” (activity slightly greater than or lesser than hepatic activity) or “strict” criteria of negativity in the assessment of metabolic response in interim studies has not, to date, shown significant differences in the prediction of the disease-free period and a better PPV (81% vs. 50%), without affecting the NPV on comparison with visual dichotomic evaluation (neg./pos.). These authors recommend calculation of the percentage of changes in the SUVmax (using the lesion most active each time) in the study of response. Nonetheless, the same studies did not show significant differences between the visual dichotomic and the semiquantitative studies when performed after the fourth cycle, suggesting that evaluation with SUVmax is more relevant in the prediction of response when the interim study is carried out early, between the first and third cycles. The use of semiquantitative criteria for the prediction of response after the second cycle requires maximum reproducibility of the results and thereby requires standardization of the method with strict review of the times of FDG injection as well as the reconstruction algorithms.

“Personalized” therapy is aimed at reducing the side effects of the treatment as well as providing alternatives to patients not responding to standard therapy. The modification of a treatment in light of the results of the interim 18F-FDG-PET/CT study may strictly be considered if the patients are in a controlled clinical study, and outside such a study the interim evaluation should only have prognostic value in the prediction of final response in both HD and DLBCL. However, in daily clinical work, that is, outside trials, this information is often taken into account to provide therapeutic alternatives to the patient.

The decision to intensify ChT regimen, perform rescue therapy or stem cell transplantation at a specific time creates a true dilemma if it is considered that the PPV may be low, especially in HD. Some studies have reported significant differences on also considering the stage of the disease. Thus, for example, an elevated PPV (>90%) is obtained in the interim 18F-FDG-PET/CT in patients with advanced HD and, to the contrary, very low values (20%) are observed in patients with earlier stages of the disease.

Taking the high NPV and the good correlation with the prognosis in the interim 18F-FDG-PET/CT study into account, these results are increasingly considered in the decision to limit the number of ChT cycles in responding patients or improve the prognosis by changing to more aggressive therapy in patients with poor response. For this reason, the incorporation of semiquantitative evaluation in F-FDG-PET/CT study into account, these results are increasingly considered in the decision to limit the number of ChT cycles in responding patients or improve the prognosis by changing to more aggressive therapy in patients with poor response.
example, the number of cycles may be reduced in patients with early stage HD treated with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) and negative interim 18F-FDG-PET/CT results or, to the contrary, if the result is positive, all the cycles of the protocol may be completed or even consolidation RDT implemented. Treatment may be intensified in patients with advanced HD with poor response in the interim study changing from ABVD to BEACOPP, and if the interim 18F-FDG-PET/CT is negative the cycles of ABVD may be completed.\textsuperscript{53}

**Follow-up with 18F-FDG-PET/CT after treatment finalization in lymphomas**

Post-treatment follow-up continues to be based on clinical evaluation, anamnesis and physical examination accompanied by the corresponding analyses. Other factors such as whether the patient is under conventional follow-up or is included in a study as well as whether the intention to treat is curative or palliative may influence the follow-up. The objective of performing new 18F-FDG-PET/CT studies in the follow-up of patients once the therapy has been completed is to achieve early detection of recurrence.

Studies describing the utility of 18F-FDG-PET/CT in the follow-up have shown contradictory results. Thus, for example, one series published by Jerusalem et al.\textsuperscript{54} showed doubtful cost-benefit profitability of follow-up with 18F-FDG PET-FDG since the appearance of an important number of false positive results requires the performance of complementary tests to determine possible relapse. To the contrary, in a study including a greater number of patients, Zinzani et al.\textsuperscript{55} found that the sensitivity of 18F-FDG-PET/CT is significantly greater than that of CT and clinical evaluation in the early detection of recurrence at 6, 12, 18 and 24 months in both HD and aggressive NHL and indolent NHL. However, they also reported an important number of false positive results (>36%) by reactive lymphadenitis and/or granulomatosis. In a recent review of the NCCN only biopsy of a hypermetabolic uptake is recommended if a new systemic treatment is considered. If the localization is solitary, not accessible or is in an unaffected basal territory, a “wait and see” attitude is recommended.\textsuperscript{55}

In the absence of large prospective studies and in light of the current results the use of serial 18F-FDG-PET/CT is recommended in the follow-up of only patients included in clinical trials.\textsuperscript{56}

The most recent review of the NCCN guidelines has established recommendations for the follow-up of patients with HD and NHL. Follow-up by clinical history and physical examination every 2–4 months over 1–2 years, every 3–6 months during the following 4–5 years and annually thereafter is proposed for patients with HD in complete initial response. For FL and those of other indolent histology in complete remission, the control would be of every 3 months during the first year, followed by 3–6 months. In DLBCL the follow-up includes this evaluation every 3 months during the first 2 years and then by studies each 6-months during the following 3 years.

Evaluation by imaging methods should be guided by the localization of the lesions at the onset as well as by the modification observed in palpable mass,\textsuperscript{39} maintaining the recommendation of performing a CT every 6 months in the first 2 years after achieving complete response in DLBCL. The routine use of follow-up 18F-FDG-PET/CT studies is not recommended once complete response has been achieved in both NHL and HD due to the possible false positive results, particularly in HD. Decisions related to patient management should not be based on 18F-FDG-PET/CT findings but rather on the clinical-pathological correlation.\textsuperscript{39,44}

**Special considerations in the treatment of lymphomas**

**Rituximab**

The use of rituximab as part of first line therapy in NHL and the validity of 18F-FDG PET in the interim study is controversial in the current medical literature.

Rituximab is the first monoclonal antibody approved for the treatment of lymphoma. It is a chimeric human-murine monoclonal antibody specific for the B-cell surface antigen, CD20, which, after administration, produces lysis of the B lymphocytes. Although its precise mechanism of action remains unknown, the induction of apoptosis, cytotoxicity mediated by cells or that dependent on antibodies have been postulated as possibilities. Numerous studies have confirmed that rituximab shows significant efficacy in NHL. This immunotherapy has the ability to sensitize chemoresistant cells which leads to the production of synergy between the two therapeutic approaches, and is the reason for its use in association with ChT in the treatment of NHL.\textsuperscript{57} All of these have resulted in the postulation that the addition of rituximab to ChT may promote an unspecific inflammatory response associated with a recruitment of immune cells at the tumor site and could carry a high rate of false positive results in the 18F-FDG-PET/CT mainly in the interim study.\textsuperscript{58} Thus, on correlating the interim 18F-FDG-PET/CT findings and progression-free survival, recent studies\textsuperscript{59,60} have shown data of sensitivity, specificity, NPV and PPV of 45–63%, 59–76%, 77–82% and 36–42%, respectively. These studies agree that, despite that need for prospective randomized studies for validation, a positive interim 18F-FDG-PET/CT after therapy including rituximab does not adequately identify the patients at high risk and therefore this technique should not be the only tool to take into account when considering changes in the therapy implemented.

**Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone**

The ABVD regimen has long been considered as the standard treatment in advanced stage HD. However, 20–30% of these patients do not achieve post therapy remission, increasing the probability of death due to recurrent or resistant lymphoma. The BEACOPP regimen is a recent, aggressive treatment that has shown high rates of progression-free survival in comparison with ABVD. However, the risk of early and late toxicity with the BEACOPP regimen is high.\textsuperscript{61}

As mentioned previously, interim 18F-FDG-PET/CT in patients with advanced HD has been evaluated in clinical trials to determine its utility as a possible prognostic predictive factor during multiple therapies, including BEACOPP. The initial therapy with BEACOPP and its interim evaluation after the fourth cycle have shown promising results, with a NPV of 98% associated with progression-free survival rates at 4 years of 96% and 78% for PET positive and negative, respectively.\textsuperscript{62} Likewise, several clinical studies have evaluated different regimens with good results in an attempt to diminish the intensity and toxicity of the treatment while continuing to achieve high rates of cure using PET as the decision making tool for the intensification of treatment.\textsuperscript{38,63,64}

**Autologous bone marrow transplantation**

Compared to standard ChT, treatment with high doses of ChT followed by autologous bone marrow transplantation increases the survival of patients with refractory lymphomas or with relapse who are still chemosensitive. 18F-FDG-PET/CT has demonstrated to be an effective tool to differentiate between responders and non-responders to this therapy, with a significant prognostic value. Thus, worse treatment results have been reported in cases which are PET/CT positive prior to transplantation, with a 3-fold greater
risk of progression and a 4-fold greater risk of death than patients presenting a negative result in the functional study. Some authors have even suggested that this pretransplant study is a more important prognostic factor than the International Prognostic Index. This principle is applicable in both HD and NHL. Comparison of the \textit{\textsuperscript{18}}F-FDG-PET/CT prior to and after autotransplantation in NHL has shown that the latter may also be considered as a prognostic factor in terms of survival.\textsuperscript{56-68}

\textit{\textsuperscript{18}}F-FDG-PET/CT in refractory lymphomas or with relapse therefore contributes to staging of the risk in terms of progression and survival but does not exclude the implementation of the treatment since high dose rescue ChT and autologous bone marrow transplantation present a curative potential and continue to be the best option for this stage of the disease.

\textit{\textsuperscript{18}}F-FDG-PET/CT in the transformation of lymphomas

The development of aggressive NHL in patients with initially indolent lymphomas has been reported in several series, estimating a risk of continuous transformation of 3% per year, up to 15 years after diagnosis. This transformation is clinically suspected by the rapid development of adenopathies, new B symptoms or a drastic increase in serum LDH levels. Despite their recognition and intensification of treatment, the prognosis is poor, with death within less than one year in most patients.\textsuperscript{69}

\textit{\textsuperscript{18}}F-FDG-PET/CT may be useful in cases with suspicion of transformation due to the different FDG avidity presented by aggressive and indolent lymphomas. In patients with a previous diagnosis of indolent lymphoma presenting foci with high metabolism in the PET/CT, transformation to a more aggressive disease should be suspected. Some investigators have attempted to determine a cut-off point of uptake to differentiate the two types, describing SUVmax thresholds >10, >13 and >17 with a certainty of 80, 90 and 100%, respectively for the presence of aggressive lymphomas. However, these lintels should be taken with caution because of the absence of wide series confirming these results and analyzing the behavior of the different subtypes of lymphoma since, for example, if the original lymphoma was follicular, SUV higher than those presented by small cell lymphocytic lymphomas or marginal zone lymphomas will be presented in the transformation.

In any case, the clinical implication of the diagnosis of transformation requires the need to always perform a confirmatory biopsy. \textit{\textsuperscript{18}}F-FDG-PET/CT has also shown to be useful here, identifying sites with greater hypermetabolism and better histological diagnostic yield.\textsuperscript{70,71}

Lastly, few publications mention the utility of \textit{\textsuperscript{18}}F-fluorothymidine PET/CT in the transformation of lymphomas. This marker of proliferative activity has shown to be greater than FDG in discriminating the aggressivity of lymphomas. However, its use is only authorized in clinical trials.\textsuperscript{72}

Learning points

\textit{\textsuperscript{18}}F-FDG-PET/CT staging of lymphomas

Lymphoma staging by \textit{\textsuperscript{18}}F-FDG-PET/CT

In the evaluation of lymphomas it should be remembered that diffuse and homogeneous bone uptake may be secondary to reactive medullar hyperplasia as may the use of colony stimulating factors (G-SCF), RDT or processes of the bone marrow itself such as myelofibrosis and should not be mistaken with lymphomatous involvement of bone marrow.

Evaluation of therapeutic response by \textit{\textsuperscript{18}}F-FDG-PET/CT

In both HD and DLBCL close to one third of the cases present a positive \textit{\textsuperscript{18}}F-FDG-PET/CT study post-therapy with a greater risk of progression or recurrence in only 60–70%. Thus, 30–40% final positive \textit{\textsuperscript{18}}F-FDG-PET/CT do not progress or demonstrate relapse, thus the need for histological confirmation prior to the initiation of rescue ChT.

Following the finalization of treatment residual mass may be observed in one third of the patients with DLBCL, with a negative \textit{\textsuperscript{18}}F-FDG-PET/CT in more than two thirds and an index of relapse of 15–20%. The residual mass observed in 70% of the patients with HD also presents negative \textit{\textsuperscript{18}}F-FDG-PET/CT results, with relapse of the disease in less than 10%.

Monitoring of lymphoma therapy by \textit{\textsuperscript{18}}F-FDG-PET/CT

The interim \textit{\textsuperscript{18}}F-FDG-PET/CT evaluation may generate information related to the prognosis of final response to ChT and/or immuno-ChT in view of the high NPV (>80% for NHL and >90% for HD). Thus, this study may be considered as an independent prognostic factor as may the baseline stage of the disease or the international prognostic score.

The adoption of liberal or strict criteria in the evaluation of metabolic response in interim studies has not, to date, shown significant differences in the prediction of disease-free periods, maintaining a good correlation with the study post-treatment.

The implementation of semiquantitative criteria (variation in SUVmax) in the evaluation is more relevant when the interim study is carried out early between the first and third cycles.

Hodgkin’s disease and aggressive NHL present greater avidity for \textit{\textsuperscript{18}}F-FDG than indolent lymphomas.

The PPV (>90%) in the interim \textit{\textsuperscript{18}}F-FDG-PET/CT in patients with advanced HD is significantly elevated and, to the contrary, very low values are obtained (20%) in patients with earlier stages of the disease.
The routine use of $^{18}$F-FDG-PET/CT is not recommended in the follow-up once complete response has been achieved in both NHL and HD due to the possible false positive results, particularly in HD. Management decisions in these patients should not be based on $^{18}$F-FDG-PET/CT findings but rather should be based on the clinical-pathological correlation.

In patients with a previous diagnosis of indolent lymphoma presenting foci with high metabolism in the $^{18}$F-FDG-PET/CT study, transformation to a more aggressive disease should be suspected.

Conflict of interests

The authors declare no conflict of interests.

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11. In patients with a previous diagnosis of indolent lymphoma presenting foci with high metabolism in the $^{18}$F-FDG-PET/CT study, transformation to a more aggressive disease should be suspected.


